

STUDIES CONCERNING THE HORMONAL CONTROL OF DECIDUOMATA AND METRIAL GLANDS

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ONE PLATE (FOUR FIGURES)

It is well known that if the uterus is traumatized while it is under the influence of active corpora lutea decidual tumors develop (Loeb, '07). A few years ago, Selye and McKeown ('35) observed that during the involution of these deciduomata, a curious organ develops on the mesometrial side of the uterus. They termed it the "metrial gland". The organ, appears to develop as a result of a curious transformation of mesenchymal cells in the endometrium, myometrium and the mesometrial attachment. It consists of large roundish cells of epithelioid appearance which are usually situated in the immediate vicinity of blood vessels around which they form thick sheaths consisting of many cell layers. The individual cells contain numerous vacuoles and in many of them, distinct coarse basophilic and eosinophilic granules may readily be distinguished. Similar cells had previously been described in the uterus of pregnant animals and women under various names such as "monster cells", "nephrophagocytes" etc. but from the earlier publications, it appears that in most animals these cells do not form a distinct organ but are scattered throughout the uterine tissue. In the rat, a definite circumscribed macroscopically visible metrial gland develops underneath the insertion of the placenta. This organ is identical, both in its macroscopical appearance and in its histological structure, with that developing outside of pregnancy during the involution of artificially produced deciduomata.

This observation led Selye and McKeown ('35) to discard the earlier theories which derived the "monster cells" and "nephrophagocytes" from fetal ectoderm (Sansom, '27; Grosser, '27; Meyer, '31).

There is no consensus of opinions concerning the function of the metrial gland. Thus some regarded its cells to be phagocytes, others who noticed their great morphological resemblance to incretory cells were tempted to consider them as having an endocrine function. It appears probable that the metrial gland may act as a holocrine-endocrine gland which furnishes nourishment to the developing embryo since many metrial gland cells are discarded into the lumen of the blood vessels and the vascular spaces in the maternal placenta become loaded with cells of the metrial gland type if the embryo is removed from a pregnant rat while the placenta is left intact (Selye and McKeown, '35). This observation may be interpreted as indicating that probably the cells are destined for the nutrition of the embryo and accumulate following removal of their normal consumer. It is quite possible, however, that in addition to this, the metrial gland may have other functions as well. For a more detailed discussion of the relevant literature the reader is referred to the above mentioned publication of Selye and McKeown ('35).

Under normal conditions the life span of the metrial gland, just as that of the placenta, is rather limited and up to the present we have no data concerning the factors responsible for its transitory existence. In the case of the placenta, it has definitely been demonstrated that the limited life span of the organ is mainly due to factors inherent in the placenta itself. Neither hypophysectomy (Selye, Collip and Thomson, '33) nor ovariectomy or removal of the embryo (Selye, Collip and Thomson, '35) interfere significantly with the normal development and eventual expulsion of the placenta from the uterus. Indeed even simultaneous removal of the hypophysis, the ovaries and all embryos does not change the life span of the placenta in a significant manner (Selye, '36). It is true that hypophysectomy or prolonged treatment with considerable

amounts of progesterone may slightly prolong the gestation period but this effect is never very marked and may be due merely to a disturbance of uterine motility. It would thus appear that the most important factors regulating the life span of the placenta are endogenous, that is, situated in the organ itself. The life span of the deciduoma on the other hand, is not endogenously regulated but dependent on the ovary. This has been demonstrated by showing that fully developed deciduomata elicited during lactation involute immediately after ovariectomy. In this respect deciduoma and placenta tissue appear to be fundamentally different (Selye and McKeown, '35).

It was deemed of interest in this connection to study the hormonal factors regulating the life span of the deciduoma and metrial gland. The fact that deciduomata may be produced in the absence of the pituitary, providing that the animals are treated with suitable amounts of estradiol and progesterone, has been demonstrated by Rothchild, Meyer and Spielman ('40) while Selye ('40 a) showed that large doses of progesterone may sensitize the uterus for the production of deciduomata even in spayed females not previously treated with estrin. These findings strongly indicate that no pituitary or ovarian hormone other than progesterone is indispensable for the production deciduomata. We do not know however what agents are responsible for the continued maintenance of these structures. It is well known that the life span of the deciduoma is limited when it is produced by uterine trauma in pseudopregnant animals, but this might be attributed merely to the fact that the progesterone production ceases at the end of the pseudopregnancy period. This explanation is not satisfactory however, because a deciduoma produced by a trauma at the beginning of the pseudopregnancy of lactation involutes much earlier than a similarly produced deciduoma elicited by trauma at a later stage of pseudopregnancy (Selye and McKeown, '35). This indicates that deciduomata elicited during the first stage of pseudopregnancy involute at a time when the corpus luteum still produces sufficient quanti-

ties of progesterone to maintain more recently produced deciduoma tissue. It should be emphasized furthermore, that although estrin is not absolutely essential for the production of deciduomata, moderate doses increase (Rothchild, Meyer and Spielman, '40) while large doses prevent (Selye and McKeown, '35) the deciduoma-forming activity of progesterone.

In the present publication, we should like to report on a series of experiments designed to study the effect of various doses of estradiol and progesterone on the life span of deciduoma and metrial gland tissue.

EXPERIMENTAL

Eleven groups of albino rats each consisting of eight females weighing 135 gm. on the average (range 103–192 gm.) were ovariectomized. Beginning 5 days after the operation, they received 10 γ of α -estradiol in 0.1 ml. of peanut oil subcutaneously bidaily on 6 consecutive days. This preliminary sensitization with estrin was identical in all animals but during the subsequent 16 days, each group received a different type of treatment consisting of varying doses of progesterone either alone or in combination with different doses of estradiol. During this second period of the experiment, all injections were again given bidaily subcutaneously, the estradiol in a solution containing 10 γ /ml. of peanut oil and the progesterone in one corresponding to 20 mg./ml. of the same solvent. In all cases both uterine horns were traumatized — on the fourth day of progesterone treatment by placing a silk thread through about one-quarter of an inch of their lumen and leaving it in this position. The formation of deciduomata was checked by biopsy on the fourth day after trauma. Ten days later the animals were killed and their uteri and mammary glands histologically examined. The results of these experiments are summarized in table 1 in which we recorded the percentage of cases in which deciduomata or metrial glands were detectable. The development and secretion of the mammary glands — as judged by their histological appearance — is indicated by a scale of + to +++++.

TABLE 1

Effect of different doses of estradiol and progesterone on the development of deciduomata, metrial glands and mammary glands.

GROUP	DAILY DOSE OF		ON FOURTH DAY AFTER TRAUMA	ON FOURTEENTH DAY AFTER TRAUMA		
	Estradiol in gamma	Proges- terone in mg.	Deciduomata positive in per cent:	Metrial glands positive in per cent:	Mammary glands	
					Development	Secretion
I	2	1	25	0	++++	++
II	2	2	50	0	++++	++
III	2	5	100	0	++++	0
IV	1	2	63	0	++++	trace
V	5	2	25	0	++++	+++
VI	15	2	25	0	++++	+++
VII	0	1	100	0	trace	0
VIII	0	2	100	50	++	0
IX	0	4	100	100	+++	0
X	0	10	100	In these two groups, injections were discontinued on the fourth day after trauma. At autopsy 14 days after trauma, the uterus and mammary glands were atrophic and metrial glands were no longer visible.		
XI	0	20	100			

Judged by the results of this first experiment, there appears to be a fairly close relationship between the doses of progesterone administered and the percentage of the animals reacting to trauma with deciduoma formation. This is clearly shown in groups I, II and III which received increasing doses of progesterone together with the same amount of estradiol. It appears furthermore that even small doses of estradiol administered concurrently with progesterone inhibit the formation of deciduomata. Thus in groups VII and VIII which received 1 and 2 mg. of progesterone deciduoma formation was much more frequent than in groups I and II which received the same doses of progesterone in combination with 2 γ of estradiol. We note furthermore, that progesterone prolongs the life span of the metrial gland, especially when it is given in large doses. Thus in group VIII, 50% and in group IX, 100% of the animals — proven to have developed a deciduoma on the fourth day after trauma — had metrial glands when examined 10 days later. We believe that the maintenance of these structures must be ascribed to the continued action of progesterone. This is shown by the fact that in the animals

of groups X and XI which were treated with daily doses of as much as 10 and 20 mg. of progesterone respectively until the day of biopsy (4 days after the trauma) but received no treatment after this date, no metrial glands were detectable on the day of autopsy. Estradiol, on the other hand, accelerates involution of the metrial gland as shown by groups II and V which received 2 mg. of progesterone in combination with small amounts of estradiol and had no remnants of metrial glands at the end of the experiment while group VIII receiving the same dose of progesterone without estradiol, showed metrial glands in 50% of the cases.

The secretion of the mammary glands appears to be directly proportional in the various groups of this series to the amount of estrin given. Progesterone causes marked development but no secretion of the gland, a fact which confirms our previous observations (Selye, '40 b). A comparison of groups II and III indicates that progesterone may actually counteract the secretory effects of a certain dose of estradiol. It should be remembered in this connection that large doses of estrin actually inhibit the lactation in animals and in women so that depending upon experimental conditions, this hormone may exert very different effects on milk production. With regard to the development of the gland, estradiol appears to synergize the action of progesterone under the conditions of the present experiment, since the breast tissue was much more developed in group I, receiving 1 mg. of progesterone with 2 γ of estradiol, than in group VII receiving the same dose of progesterone without estradiol. However this synergism may be only apparent. We noticed that in any one group of progesterone treated animals, the development of the mammary glands was less marked in those individuals in which the metrial gland persisted than in those in which this structure had involuted. Further experiments will have to prove whether this inverse relationship between the mammary and metrial glands is due to an actual utilization or destruction of progesterone by the metrial gland tissue. Meanwhile we merely wish to call attention to the possibility that the increase in the mammotropic action of progesterone, elicited

by simultaneous treatment with estradiol, may be related to the involution of the metrial gland caused by the latter.

Before accepting the conclusion, that unlike the placenta, the metrial gland may be maintained over a long period of time by continued progesterone administration, a second experimental series was designed specifically to confirm this point. Four groups of albino rats each consisting of eight females having an average weight of 85 gm. (range 73–106 gm.) were ovariectomized and subsequently sensitized with 20 γ of α -estradiol daily in the same manner as the animals of the previous experiment. After this, they received different doses of progesterone given subcutaneously in 0.1 ml. of peanut oil twice daily. The uterus was traumatized on the fourth day of progesterone treatment and the formation of deciduomata checked 4 days later by naked eye inspection after laparotomy. Distinct deciduomata were visible at this time in all animals examined, except one in the first (1 mg./day) group. The size of the deciduomata was fairly closely proportional to the amount of progesterone given. After having thus established that our treatment sufficed to elicit the formation of deciduomata, treatment was continued in all groups except one. This procedure we felt would tell us whether the life span of the metrial gland, which develops during involution of the deciduomata, can be prolonged by subsequent progesterone treatment. Table 2 summarizes the observations made after histological examination of the tissues of these animals, all of which were sacrificed 19 days following the first progesterone injection.

TABLE 2

Effect of progesterone on the maintenance of metrial glands and the development of mammary glands.

GROUP	DAILY DOSE OF PROGESTERONE IN MG.	METRIAL GLANDS POSITIVE IN PER CENT:	MAMMARY GLANDS	
			Development	Secretion
I	1	0	0	0
II	4	87 (of medium size)	++	0
III	4 (discontinued after eighth day)	0	0	0
IV	10	100 (large)	++	0

The results of the second experimental series confirmed our suspicion that the life span of the metrial gland is prolonged by progesterone. Groups II and III both received the same dose of this hormone until the deciduomata were fully developed — that is, until the fourth day after the uterine trauma — yet in group III in which treatment was discontinued after this date — all metrial glands involuted by the end of the experiment while in group II — in which injections were continued daily — the majority of the metrial glands were still well developed. This experimental series shows furthermore that, at least within the dose range of from 1 to 10 mg. per day, the maintenance of the metrial glands is directly proportional to the amount given. It is worth mentioning however, that a histological study of the traumatized area showed the typical characteristics of metrial gland tissue but excepting very rare cases almost no remnant of deciduoma tissue. It appears that even as large a dose of progesterone as that given in group IV fails to maintain the deciduomata indefinitely. In spite of such treatment these tumors degenerated and eventually became atrophic with the exception of a thin band of those cells which are situated closest to the uterine wall on the mesometrial side, that is, the cells immediately adjacent to the metrial gland area, (see plate 1).

Just as in the previous experimental series, no secretion of the mammary gland was observed under the influence of progesterone treatment in the absence of estradiol.

SUMMARY

Experiments on the rat indicate that deciduomata produced by uterine trauma in spayed females pretreated with progesterone cannot be maintained indefinitely even if large doses of this hormone are administered daily. In spite of continued treatment with as much as 10 mg. of progesterone per day, the deciduoma degenerates, with the exception of a narrow band of cells in the immediate vicinity of the uterine wall on the mesometrial side of the organ.

The metrial gland is formed in the uterine wall during involution of deciduomata. Its life span can be considerably prolonged by progesterone treatment. Indeed under the influence of this hormone, the metrial gland tissue shows definite signs of proliferation. Estradiol, on the other hand, accelerates the involution of deciduomata and of metrial gland tissue. Thus the life span of the metrial gland, unlike that of the placenta is largely dependent upon hormonal influences reaching it from other tissues, mainly the ovary.

The development of the mammary gland is greatly stimulated by progesterone in the spayed rat but this hormone elicits no milk secretion. Small doses of estradiol administered in combination with progesterone stimulate milk production. Under these conditions, the hormone proves to have a definite lactagogue effect, although it is well known that large doses of estradiol inhibit milk secretion during the normal lactation period.

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PLATE 1

EXPLANATION OF FIGURES

1 Low magnification of mesometrial side of uterus in a rat pretreated with estradiol and then receiving 10 mg. of progesterone daily over a period of 19 days. A deciduoma was produced on the fourth day of progesterone treatment by uterine trauma. The consequently developed metrial gland which forms a large bulge in the mesometrial wall of the organ is well maintained and readily visible in the lower part of the field.

2 Medium magnification of a metrial gland similar to that shown in figure 1. The portion of the deciduoma nearest to the lumen (right side of field) is completely necrotic while the narrow rim adjacent to the metrial gland (left side of field) is still well preserved. Bands of light metrial gland cells are seen traversing the field from left to right throughout the myometrium.

3 High magnification of a small blood vessel surrounded by a thick sheath of typical light metrial gland cells which contain granules. A large cell of this type is seen inside the lumen of the vessel, indicating that these elements may be discharged directly into the blood in the sense of a "holocrine endocrine secretion".

4 A single metrial gland cell as seen under oil immersion. Note the large light cell body, the well defined round nucleus and the basophilic (light) and eosinophilic (dark) granules inside the cytoplasm. The surrounding metrial gland cells are not vacuolized and consequently appear darker on the section.

